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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/045,721	10/26/2001	Naohiro Terada	5853-207	9675

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EXAMINER

KELLY, ROBERT M

ART UNIT PAPER NUMBER

1632

DATE MAILED: 11/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/045,721	Applicant(s) TERADA ET AL.	
	Examiner Robert M Kelly	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 August 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6 and 8-20 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6, 8-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's arguments of 27 August 2004 have been received and entered.

Claims 1-6 and 8-20 are pending and considered.

Claim Rejections - 35 USC § 103 – Old Rejections

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1 and 14-19 remain rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO document No. WO 99/10535 to Liu, filed 21 August 1997, published 4 March 1999, for reasons of record in the Official Actions of 10 September 2003 and 8 April 2004.

Response to Arguments – 35 USC 103 – Liu

Applicant's arguments of 27 August 2004 have been fully considered but are not found persuasive.

Applicant argues that the Claims are not limited to Liu's stem cells, but encompass totipotent stem cells, and therefore, Liu does not obviate Applicant's claims (Applicant's response of 27 August 2004, p. 5, last paragraph-p. 6, second paragraph).

Such is not found persuasive because Applicant's claims encompass Liu's stem cells. Also, Liu teaches that their invention is not limited to hematopoietic stem cells, but any stem cells where it is desired to identify agents that affect differentiation (p. 5, paragraph 2). (Official

Art Unit: 1632

Action of 8 April 2004, pp. 3-5). Moreover, Liu teaches that the stem cells embrace not only hematopoietic stem cells, but totipotent stem cells (p. 6, paragraph 3).

Applicant argues that Liu does not the steps of culturing and subculturing required by Applicant's claims and again argues that the totipotent stem cells are not taught by Liu (Applicant's response of 27 August 2004, p. 6, paragraph 3).

Such is not persuasive because this is not a rejection of anticipation, but one of obviousness, under 35 USC 103, which does not require the teaching of each and every step, but simply that the limitations are suggested. As stated in the Official Action of 8 April 2004, Liu make it obvious to (sub culture) each of the cells, exposed to different test agents, otherwise the results would mean nothing (Official Action of 8 April 2004, p. 4). Specifically, it was stated that:

[I]n view of Liu, one of ordinary skill in the art at the time of invention by Applicant (hereinafter the "Artisan") would have been motivated to identify drug candidates for promoting tissue-specific differentiation of a stem cell by providing a number of test substances (otherwise there would be no pool of substances from which to identify a substance that works), and culturing cells *in vitro* in the presence of each substance, individually, under conditions that allow for such differentiation, and analyzing the cells in the cultures for incr[e]ased tissue-specific gene expression markers. The Artisan would have been motivated to do so because Liu teaches that such screens would have use in many applications, including supportive care of cancer patients (p. 3, lines 28-30). Moreover, the Artisan would have had a reasonable expectation of success, as Liu had already shown that such screens could work *in vivo*, and culturing techniques for cells *in vitro* are routine.

(Official Action of 8 April 2004, pp. 4-5, paragraph bridging).

Moreover, as stated above, Applicant's claims encompass Liu's stem cells. Also, Liu teaches that their invention is not limited to hematopoietic stem cells, but any stem cells where it is desired to identify agents that affect differentiation (p. 5, paragraph 2). (Official Action of 8 April 2004, pp. 3-5).

Art Unit: 1632

Applicant argues that Liu does not teach sub-culturing the stem cells before administration of the test compounds, each of which have different molecular structures, to the sub-cultures (Applicant's arguments of 27 August 2004, p. 6, paragraph 4-p. 7, paragraph 2).

Such is not persuasive. Again, this is a rejection under 35 USC 103, not anticipation under 35 USC 102. It simply would not make sense to add all the test substances to one culture, then subculture, after such addition, because the results would not identify any specific compound. Applicant is confusing the cultures before and after the addition of the test compound. As Applicant's own claims subcultures are made before addition of the compound (step 1B) and cells are cultured again, in contact with the test substance (step 1C).

Applicant argues that Liu teaches away from testing any two substances against a single defined stage of differentiation, because Liu states that stem cells have to be "at different stages" of differentiation (Applicant's arguments of 27 August 2004, p. 7, paragraph 3).

Such is not considered persuasive. At the first recitation of Liu's specification (p. 17, lines 6-10), Liu is not discussing any aspect of testing compounds against multiple stages of development, but instead to testing one compound and comparing its induced gene expression against standards of different stages of differentiation. This would be comparable to Applicant's analysis of marker genes, not to administering compounds to cells at multiple stages of differentiation. The second recitation of Liu's specification (p. 4, lines 23-28) is used to support that Liu only teaches a subset of stem cells, that is: hematopoietic stem cells. This is incorrect. Although Liu teaches hematopoietic stem cells, Liu also teaches any stem cell (p. 5, paragraph 2). Therefore, Liu does not limit the invention to hematopoietic stem cells, but discusses all stem cells in general.

Art Unit: 1632

Applicant argues that Liu is an obstacle in the way of obviating the presently claimed invention because Liu teaches a laborious method requiring gene expression profiles, which are not suited for high-throughput analysis of large numbers of samples (Applicant's arguments of 27 August 2004, pp. 7-8, paragraph bridging).

Such is not found persuasive because Liu specifically defines "gene expression profile" to mean any representation of the expression of at least one mRNA species (Liu, pp. 6-7 paragraph bridging). Hence, limiting Liu to such a stringent standard for gene expression profiles is incorrect.

Applicant argues that Liu does not teach every aspect of Applicant's claims and therefore does not anticipate the claims, and hence the rejection should be dropped (Applicant's argument of 27 August 2004, p. 8, paragraph 2).

Such is not persuasive. Applicant's claimed anticipation arguments do not apply the obviousness rejection under 35 USC 103 which is presently applied, but to anticipation arguments under 35 USC 102.

Claim Rejections - 35 USC § 103 – old rejections – Liu/Moore

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Art Unit: 1632

Claims 1 and 8-13 remain rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO document No. WO 99/10535 to Liu, filed 21 August 1997, published 4 March 1999, as applied to claim 1 above, and further in view of U.S. Patent No. 5,328,844 to Moore, filed 24 June 1992, patented 12 July 1994, for reasons of record in the Official Actions of 8 April 2004 and 10 September 2003.

Response to Arguments – 35 USC 103 – Liu/Moore

Applicant's arguments of 27 August 2004 have been fully considered but are not found persuasive.

For Applicant's arguments directed to Liu, the same arguments are responded to with regard to Liu on pages 2-5 of this Office Action.

Applicant argues that Moore teaches culture media for establishing and growing and maintaining mammalian cells in culture, but not stem cells, and therefore, Moore is improperly applied, as one of skill in the art would not be motivated to combine these references (Applicant's arguments of 27 August 2004, p. 8, paragraph 4).

Such is not persuasive. Moore teaches mammalian cells, which encompass mammalian stem cells. Moreover, Moore is not required to teach the specific aspect of stem cells, because Liu teaches the subset of stem cells and culturing such stem cells (Official Action of 8 April 2004, pp. 5-7). The requirement to teach each and every aspect of the claims is limited to anticipation under 35 USC 102, not the current rejection under 35 USC 103.

Applicant argues that the Examiner is using the Applicant's specification for hindsight, and, alternatively, that no expectation of success would have been provided, because neither

Art Unit: 1632

reference teaches culturing of stem cells (Applicant's arguments of 27 August 2004, p. 9, paragraph 1).

Such is not persuasive because (i) Liu teaches the culturing of stem cells (e.g., Official Action of 8 April 2004, p. 6, paragraph 2) and (ii) the rejection does not rely on any disclosure made by Applicant (Official Action of 8 April 2004, pp. 5-7). Moreover, it would have been obvious to modify the teachings of Liu by culturing cells in microtiter plates, at 37 degrees centigrade and 7.5% carbon dioxide for 3-21 days, as taught by Moore. The Artisan would have been motivated to do so in order to allow for such cells to differentiate and express the markers of differentiation, as differentiation takes time. Moreover, the Artisan would have had a reasonable expectation of success because Moore had shown the cells able to be cultured for these time frames (Official Action of 8 April 2004, p. 7, paragraph 3).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Claim Rejections - 35 USC § 103 – old rejections – Liu/Keller

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

Art Unit: 1632

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-5 and 10-12 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Liu as applied to claim 1 above, and further in view of U.S. Patent No. 5,874,301 to Keller, for reasons of record in the Official Actions of 8 April 2004 and 10 September 2003.

Response to Arguments – 35 USC 103 – Liu/Keller

Applicant's arguments of 27 August 2004 have been fully considered but are not found persuasive.

For Applicant's arguments directed to Liu, the same arguments are responded to with regard to Liu on pages 2-5 of this Office Action.

Applicant argues that the stem cells taught by Keller are not naïve embryonic stem cells, but an embryonic stem cell line, and hence Keller cannot be applied (Applicant's arguments of 8 August 2004, p. 10, paragraph 2).

Such is not persuasive. Applicant's claims are not limited to naïve embryonic stem cells. Furthermore, Keller's embryonic stem cells are not specifically excluded by Applicant's claims. Moreover, as previously stated, Liu also teaches such ES cells without limitation to the naïve nature Applicant is arguing (p. 6, paragraph 3).

Applicant broadly argues that there is, alternatively no motivation to modify the references or reasons for success upon such modification (Applicant's arguments of 8 August 2004, pp. 10-11).

Such is not considered persuasive, as the Examiner has provided sufficient reasons to combine and expectation of success, and Applicant has failed to identify even one technical

Art Unit: 1632

aspect to overcome such statement (Official Action of 8 April 2004, pp. 8-10). Moreover, the Artisan would have been motivated to modify Liu with Keller to provide a method of screening compounds for cell growth and differentiation utilizing the embryonic stem cells as limited in Applicant's claims, and the Artisan would have had a reasonable expectation of success as Liu teaches how to define the system and Keller shows that these cells had been shown to undergo differentiation (Official Action of 8 April 2004, pp. 9-10, paragraph bridging).

Claim Rejections - 35 USC § 103 – old rejections – Liu/Thomson

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1 and 6 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Liu '535 as applied to claim 1 above, and further in view of Thomson, et al. (1998) Science, 282:1145-1147, for reasons of record in the Official Actions of 8 April 2004 and 10 September 2003.

Response to Arguments – 35 USC 103 – Liu/Thomson

Applicant's arguments of 27 August 2004 have been fully considered but are not found persuasive.

For Applicant's arguments directed to Liu, the same arguments are responded to with regard to Liu on pages 2-5 of this Office Action.

Art Unit: 1632

Applicant argues that Thomson discloses pluripotent cell lines and teaches away from embryonic stem cells (Applicant's arguments of 27 August 2004, p. 12, paragraph 2).

Such is not persuasive. These cell lines are called "cell lines" simply because they are able to maintain them in culture, they were not immortalized or otherwise altered. Moreover, Applicant's claims embrace such cells and do not specifically exclude Thomson's cells.

Applicant argues that hindsight was used for the rejection (Applicant's arguments of 27 August 2004, p. 12, paragraph 3).

Such is not persuasive, at no point in the analysis did the Examiner look to Applicant's disclosure for support in making the rejection (Official Action of 8 April 2004, pp. 10-12). Moreover, Applicant has failed to show how this rejection would be improper without Applicant's disclosure. Lastly, the Artisan would have been motivated to modify the teachings of Liu by the use of human embryonic stem cells as taught in Thomson, because Thomson teaches that such embryonic stem cells are useful for drug discovery (ABSTRACT). Moreover, the Artisan would have had a reasonable expectation of success because Thomson demonstrates these cells capable of differentiation.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Claim Rejections - 35 USC § 103 – old rejections – Liu/Thomson

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1 and 20 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Liu, as applied to claim 1 above, and further in view of U.S. Patent No. 5,143,854 to Pirrung, for reasons of record in the Official Actions of 8 April 2004 and 10 September 2003.

Response to Arguments – 35 USC 103 – Liu/Thomson

Applicant's arguments of 27 August 2004 have been fully considered but are not found persuasive.

For Applicant's arguments directed to Liu, the same arguments are responded to with regard to Liu on pages 2-5 of this Office Action.

Applicant argues that Liu does not teach gene chip technology so Liu fails to teach or disclose the claimed invention (Applicant's arguments of 27 August 2004, pp. 12-13, paragraph bridging).

Such is not persuasive. Applicant fails to address the fact this is a rejection under 35 USC 103, which only requires that the combination of references, when modified, teach or suggest each and every aspect of the claims.

Art Unit: 1632

Applicant argues that Pirrung is specifically directed to screening polypeptides and mentions polymers in general only, and therefore, does not teach Applicant's invention (Applicant's arguments of 27 August 2004, p. 13, paragraph 2).

Such is not persuasive. Applicant's claims embrace such embodiments of polypeptides, as well as other polymers. Moreover, as Applicant admits, Pirrung does teach other polymers (Id.).

Applicant argues that because Liu does not discuss gene chip technology, it would have not been obvious to incorporate the disclosure of Pirrung (Applicant's arguments of 27 August 2004, p. 13, paragraph 3).

Such is not persuasive. Pirrung was not required to disclose every applicable technology to their invention; no such requirement is made of any Applicant. Moreover, such does not rely on teachings of Liu alone, but on the teachings of Pirrung, such that every aspect of the claimed invention is taught or suggested by the art applied, or by the available knowledge to one of skill in the art (Applicant's response of 27 August 2004, p. 10, paragraph 3). The rejection of these claims in the Official Action of 8 April 2004, pp. 12-14, provides such teachings and/or suggestions.

Applicant argues that Pirrung provides no reasonable expectation of success to Liu (Applicant's arguments of 27 August 2004, p. 13, paragraph 4).

Such is not persuasive. Pirrung is not required to provide Liu with a reasonable expectation of success, but that the modified references have a reasonable expectation of success. As Liu was successful, and Pirrung was successful alone, and in the absence of reasons to doubt

Art Unit: 1632

the success of the combination of references, such reasonable expectation of success is found (Official Action of 8 April 2004, pp. 12-14).

Conclusion

Claims 1-6 and 8-20 are rejected for reasons of record.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M Kelly whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Art Unit: 1632

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert M. Kelly, Ph.D.
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ANNE M. WEHBE' PH.D
PRIMARY EXAMINER

A handwritten signature in black ink, consisting of a series of loops and a long horizontal stroke extending to the right.